BC

PATENT SPECIFICATION (11) 1412546

1412546

(21) Application No. 37589/73 (22) Filed 8 Aug. 1973
(23) Complete Specification filed 1 July 1974
(44) Complete Specification published 5 Nov. 1975
(51) INT CL² C07D 265/30 A61K 31/535
(52) Index at acceptance
C2C 1562 215 220 22Y 246 255 25Y 29X 29Y 305 30Y 364 366 368 36Y 373 37Y 462 551 613 624 628 662 66X 678 699 790 79Y QN QT

(72) Inventor EDWIN HARRY PATERSON YOUNG

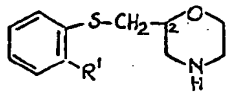
(19)

(54) MORPHOLINE DERIVATIVES

(71) We, IMPERIAL CHEMICAL INDUSTRIES LIMITED, Imperial Chemical House, Millbank, London, SW1P 3JF, a British Company, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to morpholine derivatives which possess antidepressant properties.

According to the invention there is provided a morpholine derivative of the formula:—



(I)

wherein

R^1 stands for an alkyl radical of 1 to 5 carbon atoms, an alkoxy radical of 2 to 5 carbon atoms or an aryloxy radical of up to 8 carbon atoms; and the pharmaceutically-acceptable acid-addition salts thereof.

It will be observed that the morpholine derivative of the invention possesses an asymmetric carbon atom, marked 2 in formula I, and the racemic form may therefore be resolved into two optically-active enantiomeric forms. The extent to which these enantiomers will possess the useful properties of the compound of the invention, as hereafter defined, may differ, and it is therefore to be understood that this invention encompasses the racemic form of the morpholine derivative and any enantiomorphic form which possesses such a useful property.

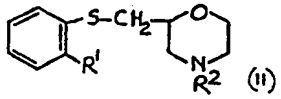
A particular value for R^1 is a methyl, ethyl, n-propyl, ethoxy, n-propoxy, n-butoxy or phenoxy radical.

A preferred value for R^1 is the phenoxy radical.

A suitable pharmaceutically-acceptable acid-addition salt of the invention is, for example a hydrochloride, hydrobromide, phosphate or sulphate, or a citrate, acetate, oxalate, methanesulphonate, toluene-*p*-sulphonate, tartrate, maleate, gluconate or resinate.

The morpholine derivative of the invention may be manufactured by methods known in themselves for the manufacture of chemically analogous compounds. Thus the following processes for the manufacture of the morpholine derivative of the formula I, R^1 having the meaning stated above, are provided as further features of the invention:—

(a) hydrolysis of a compound of the formula II:—

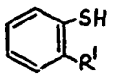


(II)

wherein

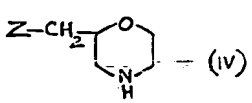
R^1 has the meanings stated above and R^2 is an alkoxycarbonyl or aryloxycarbonyl radical, for example an ethoxycarbonyl or phenoxycarbonyl radical. The hydrolysis may be carried out with a base, for example sodium hydroxide or potassium hydroxide, in a diluent or solvent, for example water, an alcohol or aqueous alcohol, for example methanol or ethanol, or dimethylsulphoxide. The hydrolysis may be accelerated or completed by the application of heat, for example at 100°C, or at the boiling point of the diluent or solvent.

(b) reaction of a compound of the formula:—



(III)

or of an alkali metal salt thereof, with a compounds of the formula:—



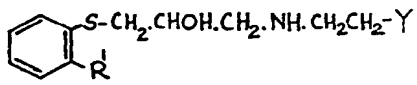
(IV)

wherein

[Price 33p]

R^1 has the meaning stated above and Z stands for a halogen atom, for example a chlorine or bromine atom, or for an alkane- or arene-sulphonyloxy radical, for example a methanesulphonyloxy or toluene-*p*-sulphonyloxy radical. The process may be carried out in a diluent or solvent, for example dimethylformamide, dimethylsulphoxide, dioxan or dimethyloxyethane, and it may be carried out at an elevated temperature, for example a temperature of up to 150°C.

(c) cyclisation of a compound of the formula:—



V

or an acid-addition salt thereof, wherein R^1 has the meaning stated above and Y is a displaceable radical, for example a halogen atom or a radical of the formula OSO_2OR^2 wherein R^2 stands for hydrogen or for an alkyl radical of 1 to 6 carbon atoms or an aryl radical of up to 10 carbon atoms, for example the methyl, ethyl, phenyl or *p*-tolyl radical, with a base. The process may be carried out in a diluent or solvent, for example water, an alcohol, for example methanol, ethanol, isopropanol, n-butanol, t-butanol or ethylene glycol, or an ether, for example diethylene ether, dimethoxyethane, tetrahydrofuran or dioxan, or a mixture of any of the abovementioned solvents; it may be carried out at ambient temperature or a temperature up to the boiling point of the diluent or solvent, for example at a temperature of between 40 and 100°C. The base may be an alkali or alkaline earth metal hydroxide for example sodium, potassium or barium hydroxide.

The starting material of the formula II for use in process (a) may be prepared, for example, by reaction of a compound of the formula III with 4-benzyl-2-toluene-*p*-sulphonyloxymethylmorpholine followed by reaction of the product with an alkyl or aryl chloroformate, for example ethyl or phenyl chloroformate.

The starting material of the formula V for use in process (c) may be prepared, for example, by reaction of a compound of the formula III with epichlorhydrin followed by reaction of the product with a compound of the formula:—

$$H_2N \cdot CH_2CH_2—Y$$

The compounds of the invention reverse reserpine-induced hypothermia in mice. The test is a standard one used in the art for determining the relative antidepressant activities in a series of chemically related compounds.

The test, known as the RHL test, is carried out as follows:—

Each member of various groups of 6 mice is given reserpine (2 mg. of base per kg. bodyweight, given subcutaneously, as the phosphate). Seventeen hours later, the gastric temperature (T_0) of each mouse is recorded by means of an orally-inserted probe coupled to an electric thermometer which is calibrated in degrees Centigrade and which can be read to 0.05°C. Immediately after the temperature measurement, the mice are dosed orally with the test compound or with saline (controls), each mouse in a group of 6 being given the same substance, and the gastric temperatures are again recorded after 4 hours (T_4). The effect of the test compound is computed from the means cumulative rise in temperature after 4 hours. The mean cumulative difference in temperature (C) is thus defined as the mean, calculated from the results obtained in mice, of the sum:—

$$T_4 - T_0$$

The effect of the test compound is related to the dose, and, using suitable doses, a dose of compound can be defined which gives a mean cumulative rise in temperature of 3°C. greater than that of control mice. This dose is called the ED_3 and is recorded in mg. per kg. bodyweight.

All the compounds exemplified in this specification are active on the RHL test at a dose (ED_3) of equal to or less than 30 mg./kg, while at the same time showing no obvious signs of toxicity.

According to a further feature of the invention there is provided a pharmaceutical composition comprising a morpholine derivative of the invention, or a pharmaceutically-acceptable acid-addition salt thereof, in association with a pharmaceutically-acceptable diluent or carrier therefor.

The composition may be in any conventional form, for example tablets, capsules, aqueous or oily solutions or suspensions, dispersible powders, sprays or aerosol formulations, and may be manufactured by conventional methods.

A preferred pharmaceutical composition of the invention is one suitable for oral administration in unit dosage form, for example tablets and capsules, which contain between 10 and 100 mg. of active ingredient, or one suitable for intravenous or intramuscular injection, for example a sterile aqueous solution containing between 1 and 4% w/w of active ingredient.

The pharmaceutical composition of the invention will normally be administered to man for the treatment or prophylaxis of depres-

sive illness at such a dose that each patient receives a total oral dose of between 150 and 400 mg. of active ingredient per day, or a total intravenous or intramuscular dose of between 40 and 80 mg. per day, the composition being administered 2 to 3 times per day.

The invention is illustrated, but not limited, by the following Examples:—

Example 1

A suspension of 4 - benzyl - 2 -(2 - n - propoxyphenylthio) - methylmorpholine oxalate (4 g.) in water is basified with sodium hydroxide solution and the free morpholine base is extracted into ether (3×50 ml.). The extract is dried ($MgSO_4$), filtered and the ether evaporated. The residual oil (3 g.) is dissolved in toluene (50 ml.) and toluene is distilled from the solution until no more water co-distils. Phenyl chloroformate (3 g.) is added and the mixture is heated under reflux for 18 hours when the solvent is evaporated. The residue of 4 - phenoxycarbonyl - 2 - (2 - propoxyphenylthio) - methylmorpholine is heated at 100°C. in a mixture of dimethylsulphoxide (30 ml.), water (15 ml.) and potassium hydroxide (5 g.) for 18 hours. The mixture is cooled, diluted with water (200 ml.) and extracted with ether (3×50 ml.). The combined extracts are dried ($MgSO_4$), filtered and the filtrate is treated with an ethereal solution of hydrochloric acid when 2 - (2 - n - propoxyphenylthio)-methylmorpholine hydrochloride is obtained which melts at 163—166°C. after crystallisation from a mixture of ethanol and ether. The 4 - benzyl - 2 - (2 - n - propoxyphenylthio)methylmorpholine used as starting material may be prepared as follows:—

2 - n - Propoxythiophenol (3.4 g.) is added to a solution of sodium ethoxide, prepared by reacting sodium (0.5 g.) with ethanol (50 ml.), and 4 - benzyl - 2 - toluene - *p* - sulphonyloxymethylmorpholine (7.2 g.) is then added. The mixture is heated under reflux for 18 hours and the solvent is then evaporated. The residual solid is stirred with water and extracted with ether (2×50 ml.). The combined extracts are dried ($MgSO_4$), filtered, and the filtrate is treated with an ethereal solution of oxalic acid to precipitate 4 - benzyl - 2 - (2 - n - propoxyphenylthiomethylmorpholine oxalate which melts at 110—114°C after crystallisation from ethyl acetate.

Example 2

A solution of 2-ethoxythiophenol (2.36 g.) in dimethylformamide (10 ml.) is added to a stirred mixture of sodium hydride (0.61 g.; 60% dispersion in oil) in dimethylformamide (50 ml.). The mixture is stirred for 2 hours at ambient temperature and then a solution of 2 - toluene - *p* - sulphonyloxymethylmorpholine (3.7 g.) in dimethylformamide (25 ml.) is added. The whole mixture is heated under reflux for 40 hours, cooled, poured into water (400 ml.) and the mixture extracted with ether (3×100 ml.). The ethereal solution is washed with water, dried ($MgSO_4$) and filtered and the filtrate is treated with an ethereal solution of hydrochloric acid when a precipitate of 2 - (2 - ethoxyphenylthio)methylmorpholine hydrochloride is obtained which melts at 219—221°C. after crystallisation from a mixture of methanol and ether.

Example 3

A solution of 2-methylthiophenol (3.03 g.) in ethanol (10 ml.) is added to a solution of sodium ethoxide prepared by dissolving sodium metal (0.56 g.) in ethanol (100 ml). The mixture is heated under reflux for 2 hours and then a solution of 2 - toluene - *p* - sulphonyloxymethylmorpholine (6.6 g.) in ethanol (25 ml.) is added and heating is continued for a further hour. The reaction mixture is cooled, the sodium toluene-*p*-sulphonate which separates is removed by filtration and the filtrate is evaporated. The residual oil is dissolved in ether (300 ml.); the ethereal solution is dried ($MgSO_4$), filtered, and treated with an ethereal solution of oxalic acid to give 2 - (2 - methylphenylthio)methylmorpholine hydrogen oxalate, m.p. 135—137°C. after crystallisation from methanol/ether.

Example 4

When the process described in Example 1 is repeated and an equivalent amount of 4 - benzyl - 2 - (2 - n - butoxyphenylthio)-methylmorpholine is used in place of 4 - benzyl - 2 - (2 - n - propoxyphenylthio)-methylmorpholine, 2 - (2 - n - butoxyphenylthio)methylmorpholine is obtained as an oil. The base is dissolved in ether and an ethereal solution of oxalic acid is added to precipitate the acid oxalate which melts at 96—98°C. when crystallised from ethyl acetate.

The starting material, 4 - benzyl - 2 - (2 - n - butoxyphenylthio)methylmorpholine, may be obtained by the process described in the second part of Example 1, replacing the 2 - n - propoxy - thiophenol by an equivalent amount of 2 - n - butoxythiophenol. The hydrogen oxalate melts at 122—125°C. after crystallisation from acetone.

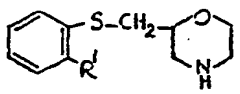
Example 5

A solution of 2 - phenoxythiophenol (1.8 g.) in ethanol (20 ml.) is added to a solution of sodium ethoxide prepared by dissolving sodium metal (0.3 g.) in ethanol (100 ml.). The mixture is heated under reflux for 1 hour, a solution of 2 - toluene - *p* - sulphonyloxymethylmorpholine (2.25 g.) in

ethanol (20 ml.) is then added and heating is continued for 48 hours. The solvent is then distilled and the residual oil is diluted with water (100 ml.), basified with sodium hydroxide solution and extracted with ether (3×50 ml.). The ethereal extract is washed with water (100 ml.) dried ($MgSO_4$), filtered and the ether evaporated. The base is treated with an ethereal solution of oxalic acid to give 2 - (2 - phenoxyphenylthio)methylmorpholine oxalate, m.p. 179—180°C. after crystallisation from methanol. The free base generated from purified oxalate by basification with sodium hydroxide solution has m.p. 88—89°C. after crystallisation from petroleum ether (b.p. 100—120°C.).

WHAT WE CLAIM IS:—

1. A morpholine derivative of the formula:—



(I)

wherein R^1 stands for an alkyl radical of 1 to 5 carbon atoms, an alkoxy radical of 2 to 5 carbon atoms or an aryloxy radical of up to 8 carbon atoms; and the pharmaceutically-acceptable acid-addition salts thereof.

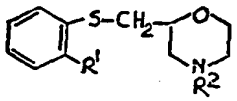
2. A morpholine derivative as claimed in claim 1 wherein R^1 stands for a methyl, ethyl, n-propyl, ethoxy, n-propoxy, n-butoxy or phenoxy radical.

3. A morpholine derivative as claimed in claim 1 wherein R^1 stands for a phenoxy radical.

4. An acid-addition salt as claimed in any of claims 1 to 3 which is a hydrochloride, hydrobromide, phosphate or sulphate, or a citrate, acetate, oxalate, methanesulphonate, toluene - *p* - sulphonate, tartrate, maleate, gluconate or resinate.

5. A process for the manufacture of a morpholine derivative as claimed in claim 1 which comprises:—

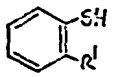
(a) hydrolysis of a compound of the formula:—



(II)

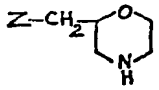
wherein R^1 has the meaning stated in claim 1 and R^2 is an alkoxycarbonyl or aryloxycarbonyl radical;

(b) the reaction of a compounds of the formula:—



(III)

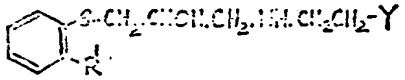
or an alkali metal salt thereof, with a compound of the formula:—



(IV)

wherein R^1 has the meaning stated in claim 1 and Z stands for a halogen atom or for an alkane- or arene-sulphonyloxy radical; or

(c) cyclisation of a compound of the formula:—



or an acid-addition salt thereof, wherein R^1 has the meaning stated in claim 1 and Y is a displaceable radical.

6. A pharmaceutical composition comprising a morpholine derivative as claimed in claim 1 in association with a non-toxic pharmaceutically-acceptable diluent or carrier.

7. A composition as claimed in claim 6 which is in a form suitable for oral administration.

8. A morpholine derivative as claimed in claim 1, substantially as described in Example 1 or 2.

9. A morpholine derivative as claimed in claim 1, substantially as described in any one of Examples 3 to 5.

J. L. BETON,
Agent for the Applicants.

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1975.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.